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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/976,560	11/24/97	FREIMER	N	UCAL-250-02U

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EXAMINER	
ARTHUR, L	

ART UNIT	PAPER NUMBER
1655	10

DATE MAILED: 01/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

Office Action Summary

Application No.	Applicant(s)
08/976,560	Freimer et al.
Examiner	**Group Art Unit**
Lisa Arthur	1655

☒ Responsive to communication(s) filed on Oct 28, 1999

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-13 and 15-24 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-13 and 15-24 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the paper filed October 28, 1999, Claims 1-7,9-11,13,15 and 16 have been amended and claims claims 17-24 have been newly added. Claims 1-13 and 15-24 are now pending. Any objections or rejections which have not been reiterated in this action from the previous action have been withdrawn as being obviated by the amendments. All of the amendments and arguments have been thoroughly reviewed but have been deemed insufficient to place this application in condition for allowance. This action is FINAL.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-13, 15,16 and newly added claims 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting an increased susceptibility for bipolar mood disorder by performing a pedigree analysis for the individual's family and analyzing the DNA from all family members for linkage of markers on the short arm of chromosome 18 between and inclusive of SAVA5 and ga203, D18S1140 and ga203, SAVA5 and W3422, S18S1140 and W3422, D18S1140 and ta201 and S18S59 and ta201 , does not reasonably provide enablement for a method of detecting a locus for bipolar mood disorder by detecting polymorphisms between and inclusive of SAVA5 and ga203 or any of the other recited markers. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims, as written, are not commensurate in scope with the disclosure in the specification because the specification has not provided sufficient guidance in light of the teachings in the art to enable the skilled artisan to detect a bipolar mood disorder susceptibility locus without undue experimentation for the reasons which follow. The art teaches that a while linkage has been shown between several different chromosomal regions and bipolar mood disorder, a susceptibility locus for this disease has yet to be identified. Stine et al. (AM J. HUM GENET. (1995) 57:1384-1394) showed evidence of linkage between bipolar disorder and markers on the short art of chromosome 18, i.e. 18p including marker D18S59 (table 1) and showed a parent-of-origin effect operating in this disease, but acknowledged that the number of loci and their precise location require further study (page 1392, col. 2). McInnes et al. (PNAS (1996) 93:13060-13065) teach that interpreting results from linkage analysis of bipolar mood disorder and other behavioral phenotypes is very difficult and often misleading because behavioral phenotypes are difficult to define, as are etiologically heterogenous and there is a lack of knowledge as to the mode of transmission of these diseases. McInnes et al concluded that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for any psychiatric disorder (page 13060, col.2, paragraph 1). However, McInnes et al. Performed a genome screening analysis for possible genes associated with bipolar disorder and found suggestive lod scores in segments of 18q,18p and 11p (see abstract and Table 1) including marker

D18S59. McInnes et al. states that the point of their study was to detect regions which merited further investigation (page 13063, col. 1, para. 1) and specifically identified the telomere of 18p as a region to further study (page 13064, col. 1, para 1). McInnes et al. States that genome screening is a first stage of a multi step process for identifying genes for complex traits (page 13064, col. 2, para. 2). McInnes et al. Taught that the second and third stages in their process were delineating clear candidate regions and fine mapping studies. Esterling et al. (MOLECULAR PSYCHIATRY (1997) 2:501-504) constructed a high resolution integrated map of 18p11.2 which is a 40cM region which they state contains a potential bipolar susceptibility locus (see Figure 1). However, even with these high resolution maps and linkage studies even as 1999 no specific polymorphisms or loci have been identified as a bipolar susceptibility locus. Ewald et al. (Psychiatric Genetics (1997) 7:1-12) teach that while chromosome 18 is one of the most promising chromosomes to contain a bipolar susceptibility locus, the research is still considered a search for susceptibility genes (see abstract). Gerson et al. (Neuropsychopharmacology (1998) 18(4): 233-242) reviewed the progress in identifying genes for manic-depressive illness and concluded that while chromosome 18 including the short arm of chromosome 18 is one of the best candidate locations for a bipolar susceptibility gene, and that the positive linkage results represent important progress, scientists are yet a long way from demonstrating disease mutations in bipolar illness (page 239, col. 2, para. 2, bottom). Nothen et al. (Molecular Psychiatry (1999) 4(1): 76-84) concluded as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may exist on chromosome 18, but

does not provide a reasonable expectation as of yet that polymorphisms in the region of 18p is associated with a bipolar susceptibility locus or what that locus will be.

The specification teaches that the marker D18S59 showed the strongest evidence for linkage to bipolar disease (page 24-25) The specification then teaches that cloned human DNA from this region, i.e. a 5cM region of chromosome 18 "is" assembled (page 25) . Markers within a 500kb and 300 kb subregion were used to delineate regions of bipolar susceptibility with the 5 cM 18pter region and blood from 105 affected individuals were tested for marker haplotypes. Figure 7 shows 18p allele frequencies and showed evidence of particular alleles being over represented on disease chromosomes. The comparisons in the figures were found to show that the region of maximal sharing between affected individuals occur between 1140t and w3442 on chromosome 18 which is a region of about 300 kb. The specification then teaches that the sequences within these regions were then analyzed for expressed sequences and sequences which are associated with bipolar disorder.

The teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field as shown by the above analysis of the prior art and because the specification has not provided evidence that would allow the skilled artisan to predict that where and what the bipolar susceptibility locus will be. The specification appears to present data defining a smaller region of the 18pter which has a higher probability of possibility

containing a susceptibility locus but the art as of 1999 still states that scientist are a long way from pinpointing a locus or polymorphisms which are predictability associated with bipolar disease. Furthermore, the claims as written are claims to a research project without a predictable outcome but which encompass the detection of a bipolar disease gene. The art makes clear that this objective is of great interest and the target of extensive research by many groups. In fact many groups are taking the same approach as described in the specification for identifying such a bipolar locus without success. The fact that the specification presents evidence of linkage to the recited markers to a smaller region than is taught by the art would provide information within families of affected individuals such that an increased risk of developing bipolar mood disorder could be predicted in a particular family member by doing a pedigree analysis using the markers disclosed int he specification and recited in the claims showing maximal sharing between affected individuals. The specification however does enable the skilled artisan to detect a bipolar mood disorder locus or polymorphisms within the recited region without undue experimentation for the reasons given above.

4. The response traverses the rejection on the following grounds. All of the arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. The response argues that McInnes et al do not support lack of enablement because their statements were directed to drawbacks of studies prior to their own. This argument is not convincing because McInnes et al. state that their work is preliminary and merits further study. While this is

certainly true, a specification is not enabling when it merely suggests that further investigatio is promising. In light of the high degree of unpredictability in finding loci which confer suceptibility to a disease such as bipolar mood disorder which is tauhgt by the cited art to be difficult to follow phenotyically and which appears to be associated with a number of different possible loci, this teaching in the art that the 18p regions merits further study , does not provide the skilled artisan with a reasonable expectation that this region will contain a loci predictably with bipolar mood disorder. The argument that Stine is not evidence of non-enablement because Stine et al. Focused on a pericentromeric region of chromosome 18 is not convincing because Stine was cited as evidence that a showing of linkage was insufficient to predict relaible association to bipolar mood disorder. The argument that Esterling et al., Eald et al. And Greson et al.do not support non-enablement because they are directed to the 18p11.2 region instead of the 18p11.3 region is not convincing becauset these references were cited to demonstrate that the high degree of unpredictability in establishing an association of a lcous or a polymorphisms to bipolar mood disorder even which high definition maps and suggestive linkage results. All of the cited references show that the results are preliminary and while promosing require extensive experimentation to identify polymorphisms associated with the disease. Nothen was cited again to demonstrate the preliminary nature of the data as late as 1999 and the requirement for undue experimetnation to practice the claimed invention.

The amendment of the claims to recite susceptibility polymorphism rather than susceptibility locus does not obviate the rejection because the specification has not taught any one

polymorphisms which has been shown to be predictably associated with method bipolar mood disroder for all the same reasons given above regarding a susceptbility locus. Therefore the claims stand rejection.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 15 and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Stine et al. (AM J. HUM. GENET. 57:1384-1394(1995)).

STINE et al. Teach an isolated polynucleotide which is marker D18S59 which they showed was linked to bipolar mood disorder. Therefore, Stine et al. Teach the claimed isolated polynucleotide because the specification taught that this marker is located within the 500kb region between SAVA5 and ga203 even though Stine et al. Did not define the 500kb region disclosed in the specification.

The response traverses the rejection on the grounds that (1) Stine is not a reference under 102(b) because it was published less than one year prior to the filing date of the provisional application on which this application claims benefit and (2) that Stine et al. Does notteach that D18S59 is linked to bipolar mood disorder.

The arguments have been thoroughly reviewed. Applicant is correct in pointing out that Stine is not a 102(b) reference. However, Stine et al. Is a refernece under 35 U.S.C. 102(a). The argument aht Stine does not teach linkage of the polynucleotide to bipolar mood disorder does not obviate the rejection because the claims are broadly drawn to polynucleotides which encompass the polynucleotides of Stine et al. The fact that Stine et al. Did not teach hat these polynucleotides have the characteristic of being linked to bipolar mood disorder is irrelevant because this characterisitc would be an inherent characteristic since the polynucleotides are the same. The discovery of the linkage does not negate the fact that Stine et al. Taught the claimed polynucleotide. Therefore, this rejection is maintained.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday-Thursday from 7:00AM to1:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

January 17, 2000